to its functioning.[8] Such skepticism is often justified: if a component does manage to function when isolated in this manner, it may function differently than in the intact cell. Second, the centrifugal forces generated by the available centrifuges were too weak to separate most cellular constituents.

Beginning in the 1920s, several researchers set about improving the capacity of the centrifuge. Swedish physical chemist Theodor ("The") Svedberg turned to centrifugation in the course of his work on colloids. Svedberg and Herman Rinde (1924) built an electrically driven centrifuge from the components of a cream separator. In addition to generating higher rotational speeds and hence greater centrifugal forces, there was a window through which the process of sedimentation during centrifugation could be observed.[9] It was this potential for direct observation that led Svedberg to refer to his centrifuge as an *ultracentrifuge*. However, the meaning of the term shifted and it came to be used for any centrifuge running at high speeds in a vacuum or near vacuum.

Independently, Elime Henriot, working in Belgium, achieved high rotational speeds with an air turbine centrifuge. Jesse Beams, together with his graduate student Edward Pickels at the University of Virginia, modified Henriot's design by introducing a larger rotor enclosed in a vacuum chamber and suspended by a steel wire (see Beams, 1938). Pickels continued to innovate with centrifuges at the International Health Division of the Rockefeller Foundation, where he collaborated with Johannes Bauer in the development of a centrifuge that could be used to separate filterable viruses. Subsequently, Pickels (1942) went on to design an electrically driven ultracentrifuge which investigators found far easier to use.

By the early 1930s the centrifuge as an instrument had been sufficiently developed that it was available for use by biologists such as Martin Behrens (1932) and Robert Bensley and Normand L. Hoerr to attempt to isolate cell structures. The results of these studies were impressive. In 1934 Bensley and Hoerr could reliably produce a fraction which they claimed, based primarily on information about the size of the component particles, was mitochondrial in nature. In the late 1930s and early 1940s, Claude could produce four distinct fractions that were clearly different in both appearance and chemical

[8] Schneider and Kuff (1964, pp. 19–20) commented, "The attitude of most cytologists was in large part responsible for the lack of consideration of isolation methods. They argued, on the basis of their observations of living cells under the microscope, that disruption of the cell wall produced immediate and irreversible changes in the cellular components."

[9] Svedberg's initial success was in sedimenting haemoglobin and demonstrating that it was a homogeneous molecule, not a heterogeneous colloid (Svedberg & Fåhraeus, 1926). This and subsequent studies helped demonstrate that proteins were in fact macromolecules.